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ORIGINAL ARTICLE

Adjunctive Diquafosol Sodium 3% and Tear-Ferning Recovery After Pars Plana Vitrectomy: An Exploratory Randomized Trial

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ABSTRACT

Background: Ocular-surface disturbance after pars plana vitrectomy (PPV) may impair tear-film stability and mucin-related function. Diquafosol sodium stimulates aqueous and mucin secretion through $P2Y_2$-receptor signaling, but evidence after PPV remains limited.

Objective: This study evaluated adjunctive diquafosol sodium 3% using tear-ferning grade as an exploratory outcome.

Methods: This single-center randomized trial enrolled 36 adults after PPV. Participants received diquafosol sodium 3% six times daily for eight weeks plus standard postoperative care (n=18) or standard care alone (n=18). Treatment was open label; tear-ferning assessment was performed by a masked assessor. Ferning grade was measured at postoperative weeks 1, 2, 4, and 8. Between-group comparisons used the Mann–Whitney U test with multiplicity adjustment, and standardized effect magnitudes were summarized using Hedges g with 95% confidence intervals.

Results: Mean ferning grades were similar at week 1 (3.94±0.236 vs 3.72±0.461; p=0.203), week 2 (3.67±0.594 vs 3.72±0.461; p=0.938), and week 4 (2.89±0.323 vs 3.00±0.000; p=0.584). At week 8, the diquafosol group had a lower mean grade than the control group (2.11±0.471 vs 2.72±0.461; p=0.003), with a standardized effect magnitude of 1.28 (95% CI 0.57–1.99). No adverse events were reported.

Conclusion: Adjunctive diquafosol was associated with better tear-ferning grade at eight weeks after PPV. The finding is exploratory and requires confirmation using larger, multicenter, placebo-controlled trials with multidimensional ocular-surface outcomes.

1. Introduction

Dry eye disease is a multifactorial, symptomatic disorder characterized by loss of tear-film and/or ocular-surface homeostasis, with tear-film instability, hyperosmolarity, inflammation, surface damage, and neurosensory abnormalities acting as etiological factors.[1] This framework is relevant after ophthalmic surgery because perioperative exposure can disturb several components of the lacrimal functional unit even when the posterior-segment objective is achieved.

Prospective studies have documented heterogeneous ocular-surface responses after vitreoretinal surgery, including reduced noninvasive tear break-up time, altered tear-meniscus measurements, epithelial disturbance, symptoms, and changes in the corneal subbasal nerve plexus.[2–4] More recent investigations have identified patient- and procedure-related risk factors for post-vitrectomy dry eye and have shown that conjunctival wound-closure technique can influence recovery.[5,6] Collectively, these findings indicate that postoperative ocular-surface change depends on baseline phenotype, surgical exposure, co-interventions, and the measurement domain.

Evidence for diquafosol after vitrectomy remains limited. A preliminary study in patients with type 2 diabetes undergoing vitrectomy reported favorable changes in several tear-film and symptom measures with diquafosol compared with sodium hyaluronate.[7] Its diabetes-specific population, active comparator, and multidimensional outcome battery differ from the present investigation, leaving uncertainty about adjunctive diquafosol in a broader PPV population assessed with tear ferning.

Recent primary studies support biological and clinical activity of diquafosol across other ocular-surface contexts. Randomized and prospective investigations after cataract surgery and in diabetes-associated dry eye have reported improvements in tear-film stability, staining, symptoms, or related ocular-surface measures.[8–10] A large phase IV study and a randomized study combining diquafosol with intense pulsed light further demonstrated measurable activity in routine and evaporative dry-eye populations.[11,12] Long-acting formulations and direct comparison with another mucin secretagogue have also produced favorable ocular-surface responses.[13,14] A 2025 randomized

study extended this evidence to corneal nerve density and tear-film outcomes in patients with diabetes.[15]

Additional recent studies show that treatment effects vary with phenotype, perioperative context, dose frequency, and outcome selection. Preoperative cataract-surgery studies evaluated refractive accuracy and intraocular-lens prediction, while other investigations examined inflammatory markers, dry eye after FS-LASIK, and post-refractive-surgery management.[16–20] Short-term tear-film dynamics have been studied in healthy participants and soft-contact-lens wearers, and comparative clinical studies after cataract surgery or against cyclosporine have assessed additional effectiveness and inflammatory outcomes.[21–24] This breadth supports plausibility but does not substitute for setting-specific evidence after PPV.

Mucins are central to ocular-surface wettability, lubrication, epithelial protection, and barrier integrity. Recent experimental work confirms that transmembrane mucin 1 restricts fluorescein ingress into corneal epithelium and that pyrimidinergic receptors on conjunctival goblet cells can increase intracellular Ca^{2+} and stimulate mucin secretion.[25,26] Comparative experimental data also support ocular-surface protection by diquafosol in dry-eye models.[27] Diquafosol is therefore more accurately described as a $P2Y_2$-receptor agonist with tear-fluid and mucin-secretagogue activity, rather than as a simple replacement lubricant.

The tear-ferning test evaluates the crystallization pattern formed after a small tear sample dries on a glass surface. Contemporary studies demonstrate that electrolyte composition and participant characteristics can alter the resulting pattern, while recent deep-learning work confirms that ferning images can be graded reproducibly when image acquisition and classification are standardized.[28–31] Tear ferning should therefore be interpreted as a complementary physicochemical tear-film characteristic, not a direct quantitative assay of MUC5AC or a substitute for symptoms, staining, osmolarity, tear volume, and tear break-up time.

The novelty of this study is its randomized evaluation of adjunctive diquafosol after PPV using standardized serial tear-ferning assessment in a broader postoperative population than the diabetes-specific vitrectomy evidence currently available.[7] The aim of the study was to compare tear-ferning grades between diquafosol plus standard postoperative care and standard care alone at postoperative weeks 1, 2, 4, and 8. The principal objective was to estimate the between-group difference at week 8; earlier visits described the emerging trajectory. We hypothesized that the diquafosol group would have a lower, more favorable week-8 ferning grade.

2. Methods

Study design and setting

This was an exploratory, single-center, parallel-group randomized trial conducted in the Department of Ophthalmology, Dr. Mohammad Hoesin General Hospital, Palembang, South Sumatra, Indonesia. Recruitment and follow-up occurred from May through December 2023. Participants were allocated in a 1:1 ratio to adjunctive diquafosol sodium 3% plus standard postoperative care or standard postoperative care alone. The protocol evaluated an eight-week postoperative treatment period. Because the control group did not receive a placebo drop, treatment administration was open label. The assessor responsible for tear-ferning grading was masked to group assignment.

The study is reported as exploratory because of the modest sample, single-center setting, and use of one ocular-surface outcome domain. The report was organized with reference to contemporary CONSORT principles for transparent reporting of randomized trials, while recognizing that the study was conducted before publication of CONSORT 2025.[32]

Participants

Adults aged 18–75 years undergoing elective PPV for a vitreous or retinal indication were screened. Participants were eligible when they had undergone PPV in the study eye, did not have preoperative dry eye requiring topical lubricant or prescription therapy, had no known contraindication to the study or postoperative medications, agreed to follow the assigned regimen, and could attend the planned visits. Each participant contributed one operated eye.

Exclusion criteria were simultaneous bilateral PPV; a corneal epithelial defect or active herpetic keratitis; severe systemic disease preventing follow-up; pregnancy or breastfeeding; use of systemic medication known to substantially affect tear function when this could not be stabilized; hypersensitivity to diquafosol, topical corticosteroids, or fluoroquinolone antibiotics; and ocular-surface surgery in the study eye during the preceding six months. These criteria were intended to reduce major alternative explanations for postoperative tear-film change while retaining a clinically representative range of PPV indications.

Forty individuals met preliminary screening criteria. Four were not randomized: two did not meet the complete eligibility criteria and two declined participation. Thirty-six participants entered the randomized comparison, with 18 assigned to each group. All randomized participants completed the eight-week follow-up according to the source records, so the reported analysis included 36 participants.

Randomization and allocation concealment

The allocation sequence was generated using computer-based block randomization with a fixed block size of four. An independent biostatistician

prepared the sequence. Assignments were placed in consecutively numbered, opaque, sealed envelopes, which were opened after eligibility and consent procedures. The fixed block size and absence of a matching placebo could potentially permit anticipation of assignments if staff became aware of prior allocations; this consideration is relevant when interpreting the exploratory findings.

Participants and treating clinicians necessarily knew whether the additional diquafosol regimen had been prescribed. The outcome assessor evaluated coded tear-ferning preparations without access to the treatment assignment. Clinical management was performed separately from grading. Only aggregate group summaries were available for the present analysis, and analyst masking could not be verified.

Interventions

Standard postoperative care in both groups consisted of topical dexamethasone 0.1%, administered four times daily for two weeks and then twice daily for two additional weeks, and topical moxifloxacin 0.5%, administered four times daily for one week and then three times daily for one additional week. These medications reflected the postoperative regimen used in the study setting.

The intervention group additionally received diquafosol sodium 3% ophthalmic solution, one drop in the operated eye six times daily for eight weeks. Suggested administration times were 08:00, 11:00, 14:00, 17:00, 20:00, and 23:00. The comparator group did not receive a placebo or additional lubricant as part of the assigned study regimen. The comparison therefore estimated the effect of adding diquafosol to the local standard-care regimen rather than the pharmacologic effect isolated from drop frequency, attention, and expectancy.

Adherence was evaluated at follow-up through review of treatment diaries and remaining study medication. The source manuscript reported mean adherence of 94% in the diquafosol group, with a range of 88%–100%. Because participant-level adherence data were not available for the present editorial analysis, adherence was described without covariate adjustment or per-protocol modeling. Participants remained in their randomized groups for the reported comparisons.

Tear-ferning assessment

The study outcome was tear-ferning grade. A small tear sample was collected from the operated eye using a standardized collection approach based on tear recovery from a Schirmer strip. The sample was placed on a clean microscope slide and allowed to dry under controlled room conditions. The source protocol specified a room temperature of 23±2°C and relative humidity of approximately 45%. Slides were examined by light microscopy and graded by one trained assessor who was masked to treatment allocation.

Ferning patterns were classified on the four-category Rolando scale: grade 1 indicated a dense, uniform fern pattern; grade 2 indicated less dense but still recognizable branching; grade 3 indicated incomplete or irregular ferning; and grade 4 indicated minimal or absent ferning. Lower grades were interpreted as more favorable tear-ferning patterns. The assessment schedule was postoperative week 1, week 2, week 4, and week 8. The week-1 measurement functioned as the earliest postoperative assessment in this report and should not be interpreted as a preoperative tear-film value.

The tear-ferning test has practical advantages but also important measurement constraints. Ferning reflects the combined physicochemical behavior of tear constituents during evaporation rather than a direct assay of MUC5AC concentration. Collection technique, sample volume, slide preparation, temperature, humidity, drying time, microscopy, and grader judgment can influence the resulting pattern.[28–31] Standardization and masking were used to reduce these sources of variability, but no duplicate reading or formal intra-rater reliability analysis was available.

Outcomes

The principal efficacy outcome for this report was the between-group difference in tear-ferning grade at postoperative week 8. Between-group comparisons at weeks 1, 2, and 4 were treated as supportive descriptions of the postoperative course. This hierarchy was used to avoid interpreting each visit as an independent confirmatory endpoint.

Safety information was collected during follow-up through clinical review and participant reporting. Events of interest included ocular irritation, conjunctival hyperemia, punctate epithelial change, and suspected hypersensitivity. Given the small sample and short follow-up, absence of an observed event was not interpreted as evidence that the treatment has no risk.

Sample size

The study used an exploratory target of 36 participants, 18 per group. The source documentation described preliminary information used during planning, but the present report does not rely on observed-effect post hoc power. With a small exploratory trial, the width of the confidence interval and consistency across outcomes are more informative than retrospective power calculations. The standardized effect estimate at week 8 is therefore presented with its 95% confidence interval.

Statistical analysis

Participant characteristics were summarized by randomized group using means and standard deviations for age and baseline ferning grade and counts with percentages for categorical variables. Significance tests were not emphasized for baseline variables because randomization, not a null-hypothesis test of baseline equality, defines the comparison.

Potentially meaningful imbalances were considered descriptively.

Tear-ferning grade is ordinal. Between-group comparisons at each visit used the Mann–Whitney U test. To limit false-positive interpretation across the three post–week-1 comparisons, a Bonferroni-adjusted threshold of 0.017 was used as a conservative reference. Standardized between-group effect magnitudes were summarized as bias-corrected Hedges g values with 95% confidence intervals, following the source statistical output. Because lower ferning grades indicate a more favorable pattern, the clinical direction was described in words rather than inferred solely from the sign convention of the standardized statistic.

No multivariable or repeated-measures model was fitted because participant-level data were unavailable for the present analysis. All p values are two-sided. Statistical calculations in the study were performed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Ethical considerations

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya. Written informed consent was obtained from all participants before enrollment. Participant confidentiality was maintained throughout data collection, analysis, and reporting.

3. Results

Participant flow and baseline characteristics

Of 40 people assessed during preliminary screening, four were not randomized: two did not fulfill the complete eligibility criteria and two declined participation. Thirty-six participants were randomized, 18 to adjunctive diquafosol and 18 to standard care. All participants completed the eight-week follow-up and were included in the randomized-group analysis, as detailed in Figure 1.

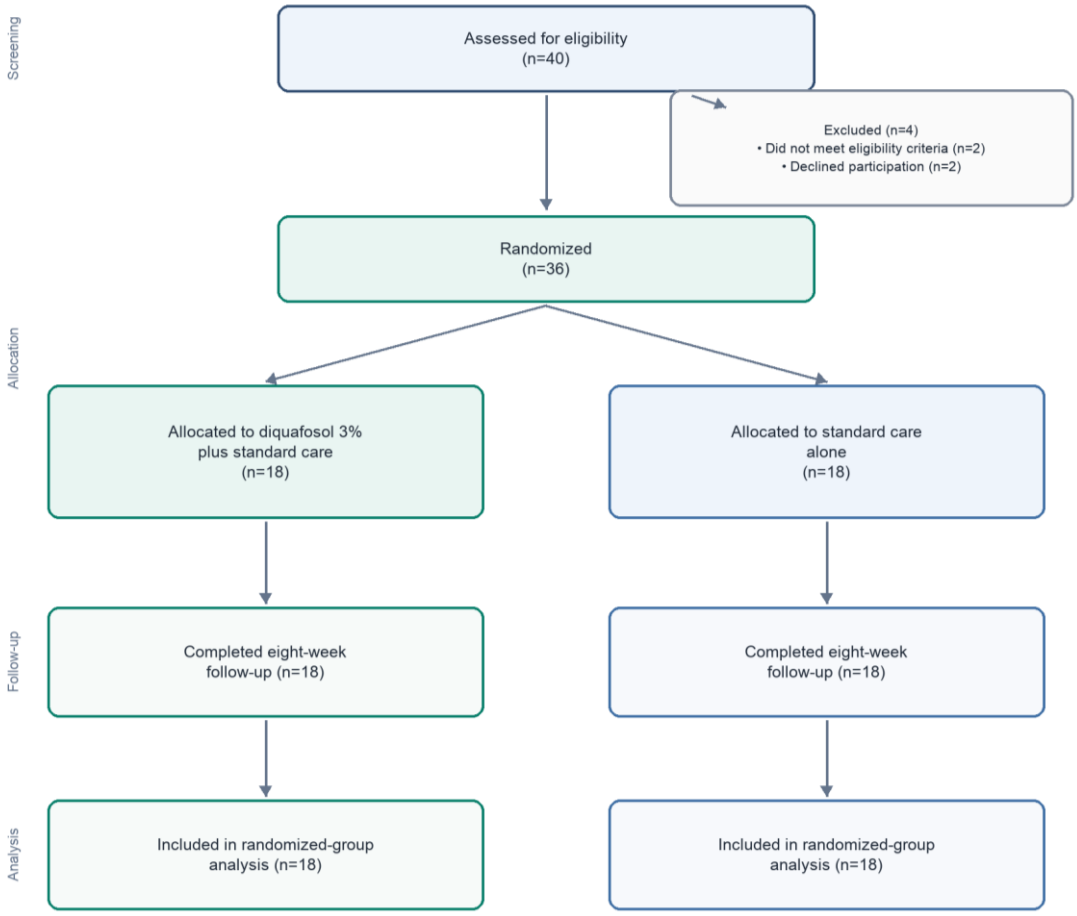

Figure 1. Participant flow through screening, randomized allocation, eight-week follow-up, and randomized-group analysis.

Baseline demographic and clinical characteristics are detailed in Table 1. Mean age was 48.7±12.3 years in the diquafosol group and 51.3±11.8 years in the control group. The intervention group included eight men and ten women; the control group included seven men and eleven women. Diabetes mellitus was present in three participants in each group, and hypertension was recorded in five and six participants, respectively. Retinal detachment, proliferative diabetic retinopathy, and other indications were represented in both groups. The mean postoperative week-1 ferning grade was numerically higher, indicating a less favorable pattern, in the diquafosol group (3.94±0.236) than in the control group (3.72±0.461).

Table 1. Baseline demographic and clinical characteristics.

Characteristic	Diquafosol (n=18)	Control (n=18)
Age, years	48.7±12.3	51.3±11.8
Male sex, n (%)	8 (44.4)	7 (38.9)
Female sex, n (%)	10 (55.6)	11 (61.1)
Diabetes mellitus, n (%)	3 (16.7)	3 (16.7)
Hypertension, n (%)	5 (27.8)	6 (33.3)
Postoperative week-1 ferning grade	3.94±0.236	3.72±0.461
PPV indication: retinal detachment, n (%)	7 (38.9)	8 (44.4)
PPV indication: proliferative diabetic retinopathy, n (%)	6 (33.3)	5 (27.8)
PPV indication: other, n (%)	5 (27.8)	5 (27.8)

Values are mean±SD unless stated otherwise. PPV, pars plana vitrectomy; SD, standard deviation.

Tear-ferning outcome

Visit-specific tear-ferning values and effect estimates are detailed in Table 2, and the descriptive group trajectories are visualized in Figure 2. At week 1, both groups had high mean grades, consistent with markedly abnormal postoperative ferning patterns. The between-group comparison was not statistically significant (p=0.203). At week 2, the mean grade was 3.67±0.594 in the diquafosol group and 3.72±0.461 in the control group (p=0.938). At week 4, corresponding values were 2.89±0.323 and 3.00±0.000 (p=0.584). Neither supportive comparison met the adjusted threshold.

Table 2. Tear-ferning grade by postoperative assessment.

Visit	Diquafosol (n=18)	Control (n=18)	Mann–Whitney p	Hedges g (95% CI)
Week 1	3.94±0.236	3.72±0.461	0.203	0.42 (−0.28 to 1.12)
Week 2	3.67±0.594	3.72±0.461	0.938	−0.09 (−0.80 to 0.62)
Week 4	2.89±0.323	3.00±0.000	0.584	−0.49 (−1.20 to 0.22)
Week 8	2.11±0.471	2.72±0.461	0.003*	1.28 (0.57 to 1.99)

*Values are mean±SD. Lower grades indicate more favorable ferning patterns. *Below the Bonferroni-adjusted threshold of 0.017. CI, confidence interval; SD, standard deviation.*

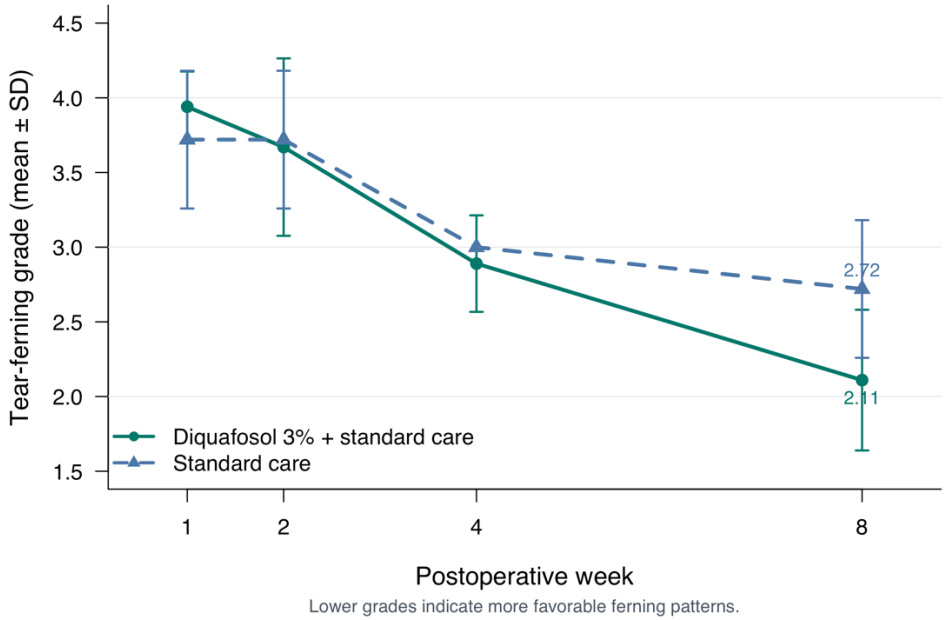

Figure 2. Mean tear-ferning grades at postoperative weeks 1, 2, 4, and 8. Error bars indicate ±1 standard deviation. Lower grades indicate more favorable ferning patterns. Connected lines are descriptive and do not represent a modeled treatment-by-time effect. The week-8 between-group comparison yielded p=0.003.

At week 8, the mean tear-ferning grade was 2.11±0.471 in the diquafosol group and 2.72±0.461 in the control group. The Mann–Whitney comparison yielded p=0.003, which was below the adjusted threshold of 0.017. The standardized effect magnitude was 1.28 (95% CI 0.57–1.99), favoring the lower grade observed with adjunctive diquafosol. The confidence interval

remained broad, consistent with the limited precision of an 18-participant-per-group study.

The group means declined over follow-up in both arms. Because the report is based on aggregate visit summaries and did not fit a treatment-by-time repeated-measures model, the visual separation at week 8 should not be interpreted as a formally estimated difference in slopes or proof of an earlier onset of action.

Safety

No adverse events were reported in either group during the eight-week follow-up. Specifically, the source clinical record did not identify ocular irritation, hyperemia, punctate epithelial erosion, or allergic reaction attributed to treatment. This observation should be interpreted in the context of the small sample, limited duration, and descriptive safety ascertainment.

4. Discussion

Principal findings

In this exploratory randomized comparison, adjunctive diquafosol sodium 3% was associated with a lower tear-ferning grade at eight weeks after PPV than standard postoperative care alone. The between-group difference was not evident in the supportive comparisons at weeks 2 and 4, whereas the week-8 comparison met the conservative multiplicity-adjusted threshold and had a large standardized effect magnitude. Both groups showed numerically lower grades over time, which is compatible with postoperative recovery, while the greater separation at week 8 suggests a possible additional effect of diquafosol.

The result should be interpreted as an estimate from a small exploratory trial rather than a definitive efficacy claim. The 95% confidence interval around the standardized effect was wide, and no participant-level longitudinal model was available to distinguish a treatment-by-time interaction from visit-specific variation. The study also did not include a placebo drop, so the comparison integrates the pharmacologic effect of diquafosol with the behavioral and expectancy effects of an additional six-times-daily regimen.

Relationship to postoperative ocular-surface evidence

The findings are biologically and clinically plausible within the broader literature on the ocular surface after posterior-segment surgery. Keratograph-based work demonstrated early reductions in noninvasive tear break-up time after vitreoretinal surgery, and a one-year confocal microscopy study documented persistent alterations in corneal subbasal nerve parameters together with ocular-surface changes.[2,3] Intervention research in patients with meibomian-gland dysfunction also showed that postoperative phenotype and treatment influence the observed response.[4] These observations support the concept that an anatomically posterior procedure can have prolonged anterior-surface consequences.

Recent prospective studies further identify variability by patient characteristics and surgical technique. A 2026 post-vitrectomy cohort described ocular-surface changes and associated risk factors, while a randomized comparison of Vicryl suturing and diathermy closure showed that the conjunctival closure approach can influence postoperative ocular-surface outcomes.[5,6] Together, these studies indicate that postoperative dry-eye manifestations depend on the compartment assessed, baseline phenotype, procedure, and management strategy. Tear ferning can therefore add complementary information but cannot represent the entire ocular-surface response.

The present week-1 grades were high in both groups, suggesting substantially altered ferning patterns soon after surgery. This is consistent with an early postoperative disturbance but does not establish its cause because the study did not include a preoperative ferning assessment in the reported dataset. Standard postoperative dexamethasone and moxifloxacin, natural healing, changes in drop exposure, and behavioral adaptation may all contribute to the downward trend in both groups. The randomized comparison is most informative at the same visit between groups, particularly at week 8, rather than as an uncontrolled within-group before-and-after interpretation.

Diquafosol and mucin-oriented tear-film support

Diquafosol activates $P2Y_2$ receptors on ocular-surface epithelial and goblet cells, stimulating fluid and mucin secretion. Recent experimental studies support the barrier role of ocular-surface mucins, demonstrate functional pyrimidinergic signaling in conjunctival goblet cells, and show protective effects of diquafosol in dry-eye models.[25–27] These actions distinguish diquafosol from a simple replacement lubricant, although downstream clinical effects still depend on ocular-surface integrity, dosing, adherence, and the cause of tear-film disturbance.

Contemporary clinical evidence spans postoperative, metabolic, evaporative, and general dry-eye settings. Studies after cataract surgery and in diabetes-associated disease reported favorable changes in tear-film stability, staining, symptoms, or corneal nerve measures.[8–10,15] Phase IV data, randomized combination therapy, long-acting treatment, and a crossover comparison of mucin secretagogues further support measurable ocular-surface activity.[11–14] These studies establish plausibility but do not directly estimate adjunctive efficacy after PPV.

The variability of response across recent studies is clinically important. Perioperative cataract investigations focused on refractive accuracy and intraocular-lens prediction, while other work examined inflammation, dose frequency, refractive-

surgery dry eye, contact-lens wear, and comparisons with cyclosporine.[16–24] Accordingly, the present tear-ferning result should be interpreted within its specific postoperative setting and outcome domain rather than generalized to every dry-eye phenotype.

The phase IV study included a substantially larger safety population than the current trial, and recent randomized or prospective studies also provide broader tolerability experience.[11,13–15] Therefore, the absence of adverse events among 18 treated participants over eight weeks is reassuring only at a descriptive level. It cannot exclude uncommon reactions or supersede larger datasets.

The most directly related study is the preliminary investigation by Du et al. among people with type 2 diabetes undergoing vitrectomy.[7] That study compared diquafosol with sodium hyaluronate and reported favorable noninvasive break-up time, tear-meniscus, staining, and symptom findings. The present trial differs in its broader PPV population, standard-care-only comparator, and focus on tear ferning. The studies are complementary: the earlier work provides multidimensional clinical measures in a diabetes-specific context, whereas the current study offers an exploratory randomized estimate for a crystallization-based tear characteristic. Neither study alone is sufficient to define routine postoperative therapy.

Interpretation of the tear-ferning outcome

Tear ferning is attractive in settings where sophisticated ocular-surface instrumentation is unavailable. A small sample, glass slide, controlled drying, and light microscopy can produce a visually gradable pattern. Recent human studies confirm that electrolyte composition, refractive status, and systemic phenotype can influence the pattern, while TearNET demonstrates that standardized images can support reproducible automated grading.[28–31] These features support use as an exploratory biomarker when collection and interpretation are tightly controlled.

Nevertheless, “mucin-specific” is too strong a description. The crystallization pattern arises from interactions among electrolytes, macromolecules, sample volume, evaporation, and preparation conditions. Tear ferning does not directly quantify MUC5AC, goblet-cell density, epithelial integrity, or patient symptoms. It is also an ordinal outcome, whereas means and standard deviations provide only a convenient summary of group patterns. A robust confirmatory study should retain the ordinal distribution, report medians and category frequencies, and analyze repeated grades with an ordinal longitudinal model.

The control group had a mean and standard deviation of 3.00±0.000 at week 4, indicating no between-participant variability in the summarized grade at that visit. This may reflect genuinely identical categories or the limitations of a coarse ordinal scale in a small sample. The absence of variability complicates standardized mean-based interpretation at that time point and reinforces the importance of rank-based comparisons and category-level reporting. Future work should archive slide images, use duplicate masked grading, quantify intra- and inter-rater agreement, and consider automated image analysis.

The week-8 standardized effect magnitude of 1.28 is large, but a standardized mean difference derived from an ordinal four-grade outcome should not be interpreted as a precise clinical threshold. The estimate is best used for planning and comparison rather than as a treatment recommendation. Clinically meaningful interpretation requires convergence across signs, symptoms, and patient-reported outcomes. A difference in ferning grade may be mechanistically interesting even if patients do not perceive improvement, while symptom benefit may occur without a parallel change in one laboratory measure.

Design and analytic considerations

Random allocation and concealed envelopes are strengths because they reduce systematic allocation differences when implemented correctly. The groups were similar in size and broadly comparable on the recorded characteristics. The diquafosol group began with a numerically higher week-1 grade, which would not obviously explain a more favorable week-8 result but could interact with regression to the mean. Because week 1 occurred after surgery and apparently after allocation, it is not equivalent to a true pretreatment baseline.

The fixed block size of four is an additional concern. Fixed blocks preserve balance in a small trial but can make the next assignment more predictable when personnel know the block size and prior allocations. Opaque sealed envelopes mitigate this risk only if they are sequentially numbered, tamper evident, opened after irreversible enrollment, and handled by personnel without influence over eligibility. Future trials should use a centralized randomization system or randomly varying block sizes and document implementation.

The absence of placebo means participants and clinicians were not masked. The original concept of single blinding is therefore most accurately restricted to outcome assessment. Six additional daily instillations may alter participant attention, adherence behavior, reporting, or exposure to the preservative and vehicle. A placebo-controlled design with identical packaging and administration frequency would separate these effects more clearly. When placebo use is impractical, outcome-assessor masking, standardized co-interventions, objective adherence capture, and blinded analysis become especially important.

The statistical approach was intentionally simplified to match the available aggregate data. Mann–Whitney tests are reasonable for independent ordinal outcomes at a prespecified visit, but separate tests do not model

within-person correlation across time or directly estimate the treatment-by-time interaction. A mixed-effects proportional-odds model would make fuller use of repeated ordinal grades if participant-level data and sample size permit. Such a model would require assessment of the proportional-odds assumption, sparse categories, convergence, influential observations, and missingness. Generalized estimating equations or prespecified rank-based longitudinal approaches could be alternatives.

The report uses Bonferroni adjustment for the three post–week-1 comparisons. This conservative method reduces false-positive risk but can also reduce power in a small study. A stronger future protocol would specify one primary time point and estimand, then treat other visits as secondary or use a global longitudinal test followed by controlled contrasts. Effect estimates and confidence intervals should be emphasized over dichotomous significance. The current week-8 p value is below the adjusted threshold, but the result remains exploratory because of the modest sample and the absence of a participant-level longitudinal model.

No multivariable analysis is presented. Randomization generally supports an unadjusted primary comparison, while covariate adjustment may improve precision when prespecified. With only 36 participants, a multi-predictor model risks instability and overfitting. A future trial could prespecify a small set of prognostic variables, such as preoperative ocular-surface status, combined cataract surgery, tamponade, PPV indication, and operative duration, provided they are measured consistently and the sample supports the model.

Clinical implications

The findings suggest that diquafosol may merit consideration as an investigational adjunct during ocular-surface recovery after PPV. They do not establish a universal postoperative regimen. Diquafosol availability, licensing, cost, frequency, preservative exposure, adherence, and individual ocular-surface phenotype differ among health systems. Six-times-daily administration is burdensome, particularly for patients simultaneously using corticosteroid, antibiotic, cycloplegic, pressure-lowering, or retinal postoperative medications.

Clinical management after PPV should remain individualized. Preoperative screening for dry-eye symptoms, meibomian-gland dysfunction, corneal staining, and tear-film instability can identify patients who may require closer follow-up. Surgical technique and postoperative medication burden should be considered. When adjunctive tear therapy is used, response should be assessed with symptoms and established clinical signs rather than tear ferning alone. The present result provides a rationale for confirmatory study, not a basis for replacing existing postoperative protocols.

The low-technology nature of tear-ferning assessment may be useful in resource-constrained research settings. However, low equipment requirements do not eliminate the need for quality control. Standard operating procedures should specify the collection device, sample volume, slide type, temperature, humidity, drying time, microscope magnification, image capture, grader training, and adjudication rules. A centralized masked reading center could reduce measurement drift in a multicenter trial.

Strengths

This study addressed a focused postoperative question using randomized group allocation and serial assessment. The comparator reflected routine care in the study setting, allowing estimation of the incremental effect of adding diquafosol. Allocation concealment was planned through opaque sequential envelopes, and tear-ferning grading was separated from clinical treatment and masked to assignment. Complete reported follow-up avoided attrition in the aggregate analysis. The eight-week schedule captured both early postoperative disturbance and a later recovery point, while the primary analysis focused on the week-8 comparison and treated earlier visits as supportive.

The study also explored an outcome not routinely used in vitrectomy research. Tear-ferning patterns may capture a physicochemical aspect of the tear film that differs from tear volume, break-up time, staining, or symptoms. This mechanistic orientation is potentially valuable when aligned with a broader ocular-surface battery.

Limitations

Several limitations restrict inference. First, the sample included only 36 participants from one tertiary center. Effect estimates are imprecise, and uncommon adverse events could not be detected. The PPV indications were heterogeneous, and the report lacks detailed stratification by gauge, tamponade, combined phacoemulsification, operative duration, suturing, and perioperative ocular-surface exposure. These variables may affect recovery and limit transportability.

Second, treatment was open label because no placebo was used. Participant expectations and the behavioral effect of additional drops cannot be separated from pharmacologic action. Outcome-assessor masking reduces but does not eliminate bias. The fixed block size may also have made allocation more predictable if implementation safeguards were imperfect.

Third, week 1 was the earliest postoperative assessment rather than a preoperative measurement. The study therefore cannot quantify the magnitude of surgical change from the patient's preoperative state or confirm that groups had identical preoperative ferning patterns. The numerically higher week-1 grade in the diquafosol group introduces potential regression-to-the-mean effects.

Fourth, tear ferning was the sole reported efficacy domain. No simultaneous Ocular Surface Disease Index, symptom scale, tear break-up time, Schirmer test,

osmolarity, staining, meibography, impression cytology, or direct mucin assay was available. The study cannot establish whether the ferning difference corresponds to symptoms, epithelial health, tear volume, or MUC5AC concentration. The single-grader approach lacked formal reliability testing.

Fifth, the outcome is ordinal but was summarized with means and standard deviations, and the available aggregate data did not support a repeated-measures ordinal model. The analysis estimates visit-specific group differences rather than a longitudinal treatment effect. The standardized effect magnitude should therefore be interpreted as exploratory.

Sixth, the sample-size basis was exploratory, and post hoc power was intentionally not used. Finally, safety ascertainment was descriptive, follow-up lasted eight weeks, and no conclusion can be drawn about long-term efficacy, adherence, or tolerability.

Future research

A confirmatory trial should use a prespecified protocol and statistical analysis plan. Central randomization with concealed, varying block sizes and an identical placebo would strengthen masking. Stratification could be considered for combined cataract surgery, tamponade, pre-existing dry eye, diabetes, and PPV indication. The sample size should be based on a prespecified clinically meaningful ordinal or patient-reported difference, expected category distribution, attrition, and the chosen longitudinal model.

Outcomes should combine tear-ferning grade with validated symptoms, noninvasive tear break-up time, staining, tear meniscus measures, osmolarity, and, when feasible, impression cytology or mucin assays. Preoperative assessment is essential. Follow-up beyond eight weeks would clarify whether treatment accelerates recovery, produces a sustained difference, or merely shifts the timing of a process that ultimately converges.

The statistical plan should define one primary estimand, preserve randomized-group analysis, address missing data, and use an ordinal mixed-effects or other appropriate repeated-measures model. Reporting should include category distributions, adjusted and unadjusted effects, 95% confidence intervals, adherence, protocol deviations, and systematic adverse-event collection. Trial reporting should follow CONSORT 2025.[32]

5. Conclusion

In this exploratory randomized trial, adjunctive diquafosol sodium 3% was associated with a more favorable tear-ferning grade at eight weeks after PPV than standard postoperative care alone. Earlier between-group differences were not statistically significant, and the result does not establish an accelerated longitudinal recovery trajectory. The finding supports further investigation in a larger, multicenter, placebo-controlled trial that incorporates preoperative assessment, repeated ordinal modeling, symptoms, established ocular-surface signs, direct mucin-related measures, and longer follow-up.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya. Written informed consent was obtained from all participants before enrollment.

Conflict of interests

The authors declare that there are no competing interests.

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Author contributions

RA conceived and designed the study, performed the surgical procedures, and supervised the work. PP contributed to the study design, tear-ferning assessment and classification, and data interpretation. RY performed the data collection, statistical analysis, and manuscript preparation. All authors reviewed and approved the final version of the manuscript.

Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Generative AI disclosure

The authors declare that no generative artificial intelligence tools were used in the design, analysis, or writing of this manuscript.

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